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Central Venous Oxygen Saturation above 75% on Day Three of Septic Shock is Associated with Tripled Mortality

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Abstract

Background: Central venous oxygen saturation ($ScvO_2$) is commonly used to identify global oxygen uptake-delivery mismatches. A level above 70% was the declared goal in early resuscitation of septic shock for over a decade. Recent evidence leads to doubts and levels higher than 80% may represent harmful conditions. This study ´s aim was to identify favourable $ScvO_2$ levels in treatment of septic shock.

Methods: Electronic data of patients suffering from septic shock who have been admitted to the surgical intensive care unit of a university hospital were analysed surveying a period of six years with focus on the association of $ScvO_2$ levels with in-hospital mortality.

Results: Data from 238 individuals were included. No difference was found comparing initially measured values of $ScvO_2$ of survivors to non-survivors. Patients whose levels of $ScvO_2$ never exceeded 70% (n=28) had a higher mortality rate (73.2% *vs.* 54.3%, p<0.05). On day three patients with values above 75% (n=32) had higher mortality rates (59.4% *vs.* 38.5%, p<0.05). A mortality rate of 100% was detected if $ScvO_2$ levels exceeded 84% (n=6).

Conclusions: $ScvO_2$ develops from a therapy guiding parameter to a prognostic marker. Reaching levels of at least 70% within the first 72 h of disease is favourable in regard to prognosis. Exceeding 75% after day two is associated with higher mortality. These findings require further confirmation. At this point it can be assumed that a varying, time-dependent $ScvO_2$ approach might be required for clinical decision-making.

Keywords: Central venous; Saturation; Mortality; Septic shock; Prognosis

Introduction

Despite intensive efforts of improving therapy in treatment of septic shock mortality rates are still reported about 36.5% [1]. A number of 5.3 million deaths annually worldwide is estimated [2]. Treatment recommendations [3,4] focus on infection control and cardiorespiratory resuscitation to restore oxygen supply, optimize tissue perfusion, avoid hypoxia, and at least prevent organ failure [5]. Central venous oxygen saturation ($ScvO_2$) and serum lactate concentration are commonly accepted indicators of oxygen supply and global oxygen balance [3,6,7] and have been suggested as goals of treatment for more than a decade. Serum lactate has traditionally been interpreted as a marker of tissue hypoxia due to inadequate oxygen delivery. Particularly during prolonged episodes of sepsis, however, high levels of serum lactate can also result from impaired hepatic clearance or increased pyruvate production which is irresponsive to an optimized oxygen supply [8]. By now there are doubts concerning treatment strategies which are focused on serum lactate levels [9].

A level of $ScvO_2$ above 70% has been a conventional goal in early septic shock therapy since first early goal directed therapy (EGDT) studies have been released [10,11]. Recent trials failed to demonstrate a survival benefit for these classic treatment goals compared to usual care [12-15]. Particularly in later stages of disease, interpretation of $ScvO_2$ is challenging for clinicians [7]. Reviews attest "no benefit of early resuscitation guided by venous oxygen saturation" [16] or suggest that a subset of patients could benefit [15]. Consequently, adjusting $ScvO_2$ is no longer part of the current surviving sepsis campaign (SSC) guidelines [4]. In contrast, the SSC guidelines state that the use of the previous targets is still safe and may be considered as no harm was associated with the interventional strategies and clinicians still need guidance for approaching this group of patients with significant mortality and morbidity. This raises the question whether $ScvO_2$ should still be measured in septic shock at all.

$ScvO_2$ values are considered to reflect mixed venous oxygen saturation (SvO_2) [11]. SvO_2 is an indirect index of global oxygen supply-to-demand ratio [11]. In early septic shock with inadequate oxygen delivery, mostly due to anaemia, absolute or relative hypovolemia, or myocardial dysfunction, systemic extraction ratio rises and SvO_2 decreases [17]. In prolonged septic shock oxygen utilization is compromised by oedema induced diffusion limitation and by toxic respiratory chain uncoupling [5,18,19]. As a result less oxygen is consumed and returned back to the central circulation as indicated by increasing SvO_2 values. Increased risk of multiple organ dysfunction and death, hence, are likely reflected by both low and high $ScvO_2$ values. This suggests there may be ranges or corridors of $ScvO_2$

values, which are associated with favourable patient outcome. Moreover, the significance of specific $ScvO_2$ values may vary in the course of septic shock and thus a single fixed goal or corridor may be inadequate for treatment guidance. Data supporting these hypotheses are scarce, retrospective analyses suggest reduced survival for patients with venous saturations below 70% and above 90% in the first 6 h [19], as well as above 80% up to day three of septic shock therapy [20]. Prognostic studies evaluating $ScvO_2$ with a time-dependent approach, however, are lacking.

The aim of this study therefore was to link the level of $ScvO_2$ with mortality rates and identify $ScvO_2$ levels in defined time corridors potentially beneficial for patient outcome from septic shock.

Materials and Methods

This investigation is single centre retrospective observational, using the patient data management system (PDMS) database (IntelliVue Clinical Information Portfolio, Phillips Healthcare, Netherlands) of a surgical intensive care unit (ICU). The study is designed corresponding to the declaration of Helsinki and ethical approval has been granted by a local committee (Medical Faculty of Mannheim, Germany, chairman Prof. JP Striebel, No. 2014-816R-MA). Design and reporting are according to the CONSORT statement recommendations (www.consort-statement.org).

Cohort inclusion and exclusion criteria

All patients admitted with septic shock between 1st January 2007 and 31st October 2013 were included (Figure 1). Septic shock was operationalized according to the SSC guidelines of 2012 focussing on sepsis-induced hypotension despite appropriate volume resuscitation [3].

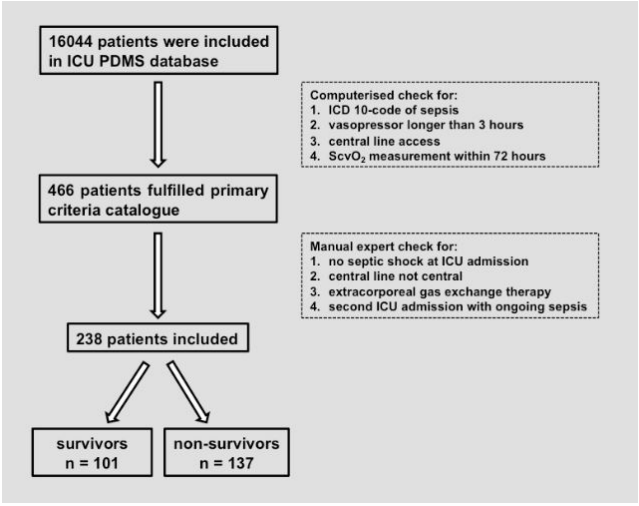

Figure 1: Flow-chart diagram of patient selection process. ICU: Intensive care unit; PDMS: Patient data management system; ICD: International statistical classification of diseases and related health problems; $ScvO_2$: Central venous oxygen saturation.

Patients admitted to the ICU with an International Classification of Disease 10-code implying sepsis who had received norepinephrine and at least one measurement of $ScvO_2$ within 72 h after ICU admission were identified automatically from the PDMS. Afterwards all matching electronic records as well as additional clinical data were examined by a medical expert. Clinical records of previous ICU stays were also reviewed. Patients who were readmitted due to ongoing septic disease were excluded as well as cases in which septic shock developed after admission to the ICU. Patients treated with norepinephrine for less than 3 h after having received a fluid bolus, whose venous catheter was not centrally located, or who have been receiving extracorporeal gas exchange therapy within their first 72 h were also excluded.

Cohort characteristics and outcome

Of all patients meeting the cohort of septic shock basic demographic data, sequential organ failure score (SOFA) and simplified acute physiology score 2 (SAPS 2) [21,22] were extracted from the PDMS. $ScvO_2$ measurements as well as hemodynamic monitoring parameters and routine laboratory parameters have been determined five times – first 6,7 to 12,13 to 24,25 to 48 and 49 to 72 h after ICU admission. If more than one value was available, the one closer to the upper time interval limit was considered with exception of the first interval in which first measurements were considered. This procedure allowed comparability to previous investigations [19,23-26]. Based on recent literature [10,20] and our receiver operating characteristic (ROC) analysis, $ScvO_2$ levels of each time interval were categorized as below, within or above corridors of 66-75% and 71-80%. Furthermore, the minimum and maximum $ScvO_2$ values during the first 72 h were extracted.

Necessity of organ replacement therapy as well as ICU length of stay were also determined. Follow-up ended at hospital discharge or in-hospital death, which were extracted from the local hospital information system (IS-H med, SAP-Industry Solution, Germany).

Note on clinical practice during the investigation

Moderate sedation, lung protective ventilator settings supporting spontaneous breathing, empirical antibiotics, early microbiological and radiological diagnostics as well as interventional and surgical focus control were ensured like recommended by the SSC [3]. For hemodynamic stabilization balanced crystalloid solutions, norepinephrine and dobutamine were preferred choices. A MAP of>65 mmHg, urine output of >0.5 ml/kg/h, $ScvO_2$>70% and serum lactate concentration<2 mmol/l were declared as primary goals. If required, hemodynamic monitoring was augmented by echocardiography or pulse contour cardiac output (therapeutic aim: cardiac index (CI)>2.5 l/min^*m^2) and to estimate volume status and contractility. $ScvO_2$ measurements were part of routine care, determined by a point-of-care blood gas analyzer (ABL800 Radiometer, Copenhagen, Denmark) and directly transmitted to the local PDMS.

Statistical analyses

Descriptive statistics were used to summarize demographic, clinical, hemodynamic and laboratory parameters of the cohort and also for survivors and non-survivors separately. Characteristics of the latter two groups were compared with two-tailed t-tests and chi-square tests. Survivors and non-survivors of the cohort were classified according to their $ScvO_2$-level at each time interval. For each of the fivetime intervals, odds ratios (OR) with 95% confidence intervals (CI) for $ScvO_2$-dependent mortality risk in those still alive at the beginning of the respective interval were obtained from logistic regression. ROC-curves were used to determine the maximum value for the sum of

sensitivity and 1-specificity of potential $ScvO_2$ cut-off values for mortality prediction at the different time intervals. The probability of survival for different $ScvO_2$ levels was depicted in Kaplan-Meier plots. For all analyses a p-value<0.05 (two-tailed) was considered statistically significant. SAS 9.4 (SAS Cooperation, Cary, North Carolina, USA) was used for data analysis.

Results

Of 16044 ICU admissions during the study period 466 potential shock patients fulfilled the inclusion criteria. After examination by an expert the final cohort of 238 patients with septic shock on admission was set (Figure 1). Overall hospital mortality of 57.6% and observed disease severity of the first day after ICU admission based on SAPS 2 and SOFA score in these patients are consistent with manifest multiple organ failure (Table 1). Survivors had higher haemoglobin levels at day one (p<0.05) and lower plasma lactate levels in any time interval (p<0.05 for each interval). A nonsignificant trend to higher initial $ScvO_2$ measurement values in survivors compared to non-survivors (mean ± SD: 75.7% ± 9.1% *vs.* 73.1% ± 10.1%, p=0.13; median: 77% *vs.* 74%) and lower ones on day three (71.2% ± 7.7% *vs.* 73.1% ± 11.6%, p=0.37; median: 72% *vs.* 75%) was detected (Figure 2).

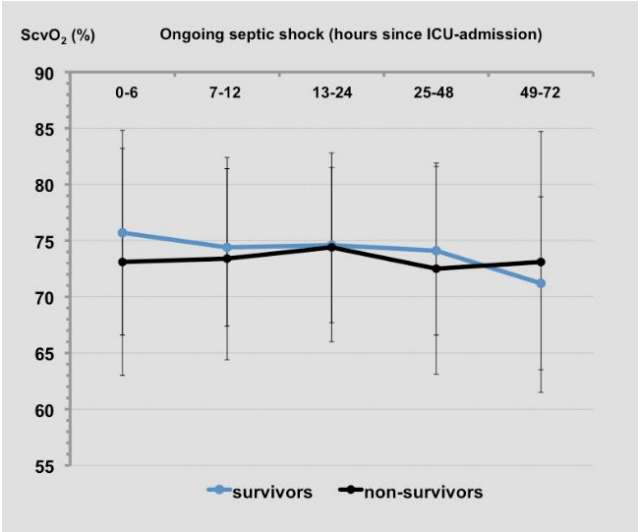

Figure 2: Development of central venous saturation in septic shock. Graphical illustration of central venous saturation development of patients under ongoing septic shock treatment – survivors are displayed in blue, non-survivors in black; dots indicate mean value and error bars standard deviations; $ScvO_2$: Central venous oxygen saturation.

	All patients	Survivors	Non-survivors	p-value
n	**238**	**101**	**137**	
Gender male (%)	159 (77)	67 (76)	92 (77)	0.89
Age – years	64 ± 15	59 ± 16	67 ± 14	<0.0001*
Medical history:				
Diabetes (%)	48 (20)	19 (19)	29 (21)	0.63
Hypertension (%)	114 (48)	49 (49)	65 (47)	0.87
Impaired immunity (%)	22 (9)	10 (10)	12 (9)	0.76
Malignancies (%)	66 (28)	18 (18)	48 (35)	<0.01*
Focus side:				
Abdomen (%)	115 (48)	45 (45)	70 (51)	0.32
Lung (%)	82 (34)	37 (37)	45 (33)	0.54
Urogenital (%)	11 (5)	8 (8)	3 (2)	<0.05*
Soft tissue (%)	10 (4)	3 (3)	7 (5)	0.42
Others or unknown (%)	20 (8)	8 (8)	12 (9)	0.82
Clinical data:				
SAPS 2	65.8 ± 14.6	61.4 ± 14.2	69.7 ± 13.9	<0.001*
SOFA	13.3 ± 2.5	12.5 ± 2.3	14.0 ± 2.5	<0.0001*
Temperature (°C)	36.9 ± 1.2	37.0 ± 1.0	36.8 ± 1.3	0.52
CRP (mg/l)	205 ± 108	196 ± 101	214 ± 113	0.44
PCT (mg/l)	22.5 ± 44.5	30.8 ± 55.9	16.8 ± 34.1	0.12
Bilirubin (mg/dl)	1.2 ± 1.2	1.2 ± 1.4	1.2 ± 1.0	0.85
Creatinine (mg/dl)	2.2 ± 2.2	2.2 ± 2.6	2.2 ± 1.8	0.91
Haemoglobin (g/dl)	10.3 ± 1.9	10.7 ± 1.9	9.9 ± 1.8	<0.05*
MAP (mmHg)	76 ± 14	77 ± 14	74 ± 13	0.37
Heart rate (/min)	106 ± 21	105 ± 20	107 ± 22	0.52
Cardiac index (l/min/m2)	3.7 ± 1.3	4.1 ± 1.4	3.4 ± 1.2	0.22
Fluid balance first day (l)	+ 6.8 ± 5.0	+ 6.8 ± 4.9	+ 6.8 ± 5.0	0.93
Norepinephrine (mg/kg/min)	0.37 ± 0.43	0.33 ± 0.37	0.39 ± 0.48	0.41
Lactate (mmol/l)	3.7 ± 3.5	2.8 ± 2.5	4.4 ± 0.5	<0.05*
SaO2 (%)	95.2 ± 4.6	95.8 ± 3.4	94.9 ± 5.3	0.12
ScvO2 (%)	74.3 ± 9.8	75.7 ± 9.1	73.1 ± 10.1	0.13
Mechanical ventilation (%)	222 (93.3)	93 (92.1)	129 (94.2)	0.53
Renal replacement (%)	46 (19.3)	12 (11.9)	34 (24.8)	<0.05*
ICU days	14.1 ± 18.0	17.6 ± 18.6	11.3 ± 17.0	<0.01*
Hospital days	30.6 ± 45.5	49.0 ± 46.3	17.0 ± 39.7	<0.0001*

Table 1: Study population – basic characteristics. First six hours data are shown except for clinical scores (first day). Data are given as number and percentage or mean ± SD, respectively; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment score; CRP: C-reactive protein; PCT: Procalcitonin; MAP: Mean arterial pressure; SaO_2: Arterial blood oxygen saturation; $ScvO_2$:

Central venous oxygen saturation; * significant result by two-tailed t-test comparison.

The minimum value of $ScvO_2$ was 69.03% on average in all patients (range 35.2%-95.3%). While $ScvO_2$ minima did not differ in survivors and non-survivors, maximum $ScvO_2$ values, on average, were significantly higher in survivors compared to non-survivors (Figure 3a). Hospital mortality was higher if maximal $ScvO_2$ values recorded at any time within the first three days of therapy were below 70%, whereas no impact on outcome was detected for maximum values ≥ 80% (Figure 3b).

Figure 4 displays mortality rates in relation to increasing $ScvO_2$ cut-off values in the period of the first 72 h. In early phases of septic shock mortality was higher in patients having lower $ScvO_2$ values up to a cut-off of 80%. These differences were not statistically significant.

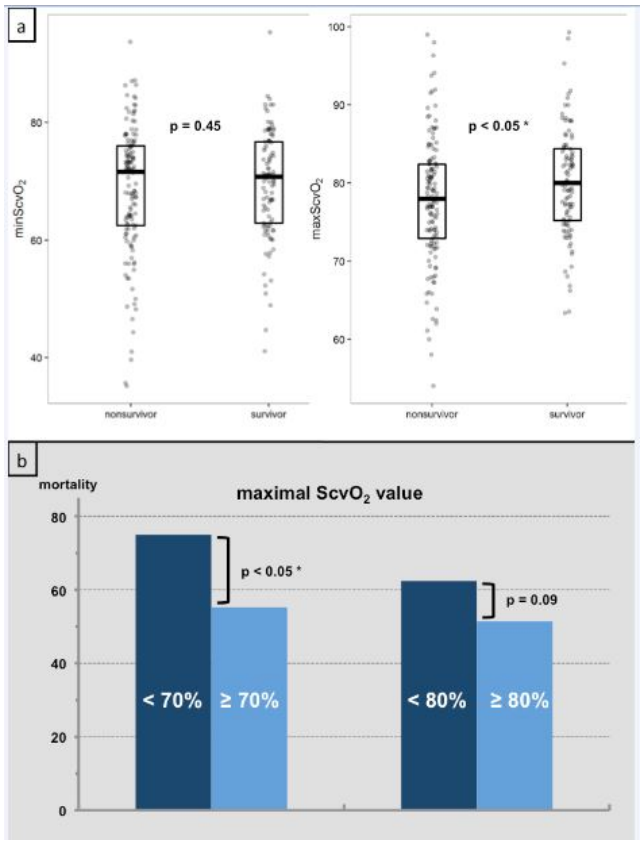

Figure 3: Minimal and maximal $ScvO_2$ values analyses. (a) Distribution of survivors' and non-survivors' minimal and maximal $ScvO_2$ values determined within the first 72 h of ICU stay; * significant result from a two-tailed t-test. (b) Mortality rates of septic shock patients classified by two different cut-off values for maximum $ScvO_2$ in the first 72 h; n=28 with maximum $ScvO_2$<70%, n=105 with maximum $ScvO_2$ ≥ 80%; * significant result from chi-square test. $minScvO_2$: Minimum central venous oxygen saturation; $maxScvO_2$: Maximum central venous oxygen saturation.

On day three $ScvO_2$ cut-offs above 70% distinguished well between survival until patient's discharge from hospital and intra-hospital mortality (Figure 4). A ROC analysis detected an optimal cut-off at 76.0% for third day's $ScvO_2$ (70.4% sensitivity, 60.6% specificity; area under the curve: 0.662). $ScvO_2$ ≥ 84.0% (n=6) on day three identified non-survivors with a sensitivity of 100%.

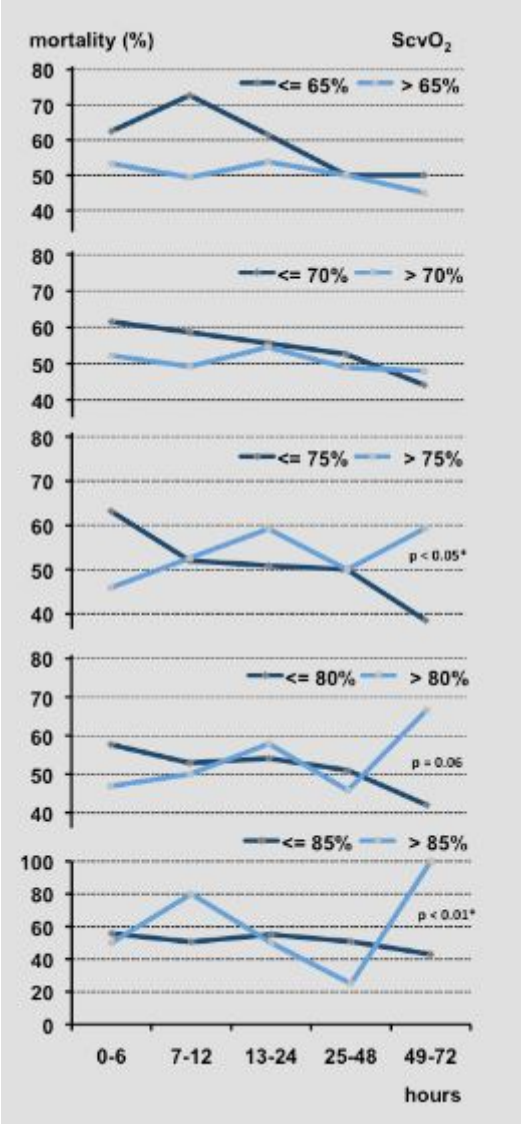

Figure 4: In-hospital mortality in dependence of variable $ScvO_2$ cut-offs. Comparative representation of in-hospital mortality in dependence upon $ScvO_2$ cut-off values over time course of ICU stay–patients with $ScvO_2$ values below the respective limit are shown in deep blue, those above the limit in light blue; $ScvO_2$, central venous oxygen saturation; *Significant result from chi-square test.

Odds ratios for in-hospital mortality of patients classified in defined $ScvO_2$ corridors (66-75% and 71-80%) did not indicate any difference regarding mortality risk for patients with $ScvO_2$ values below or above these reference limits at the times of measuring within 48 h after ICU admission (Figure 5). Mortality was higher in patients with $ScvO_2$ values>75% (n=32) compared to those in the corridor of 66–75% (n=28) on day three with an odds ratio of 3.6 (95% confidence interval

1.2 to 10.8, p=0.02). Kaplan-Meier analyses of both mentioned corridors on day three of septic shock treatment are presented as Figures 6a and 6b.

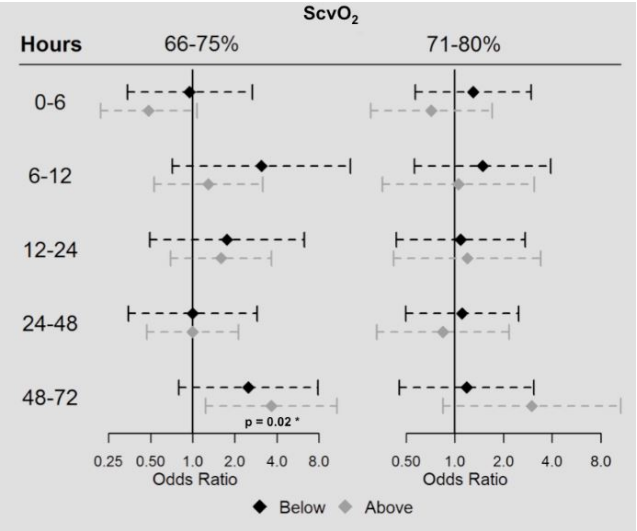

Figure 5: Forest plot of third days odds ration analyses. Forest plot of odds ratios for non-surviving in dependence upon $ScvO_2$ ranges and time intervals of ICU stay; $ScvO_2$: Central venous oxygen saturation; *Significant result.

Discussion

Based on early EGDT studies [10,27] former treatment recommendations supported $ScvO_2$ correction above a value of 70% within the first 6 h of sepsis [3,15]. In accordance Pope et al. [19] reported mortality rates to be significantly elevated if septic patients in the emergency department indicated maximum $ScvO_2$ values below 70% (hypoxic range) compared to those being in normoxic range ($ScvO_2$ 71-89%). Park et al. confirmed these findings for septic shock patients exhibiting oxygen extraction ratios higher than 0.3, being approximately equivalent to calculated $ScvO_2$ values lower than 70% [28] and Lee et al. also found reduced survival if $ScvO_2$ could not be raised above 70% and lactate remained abnormal [29]. In line with these observations, our data showed diminished survival rates if $ScvO_2$ values could not be increased above this threshold (<70%) during the first 72 h of ICU stay. About one third of our patients have had $ScvO_2$ values below 70% and approximately in one fifth $ScvO_2$ was below 65% when first measured in ICU. These results are supported by findings of Boulain et al. who prospectively showed that $ScvO_2$ values<70% are frequent (27%) at ICU admission [30] and extended by van Beest et al., who demonstrated that even lower rates of $ScvO_2$ (<60%) are still occurring (6%) [25]. Initial mean $ScvO_2$ values (74% ± 11% [25] and 74 ± 10.4% [30]) were comparable to ours and there was also no difference detected between survivors and non-survivors [30].

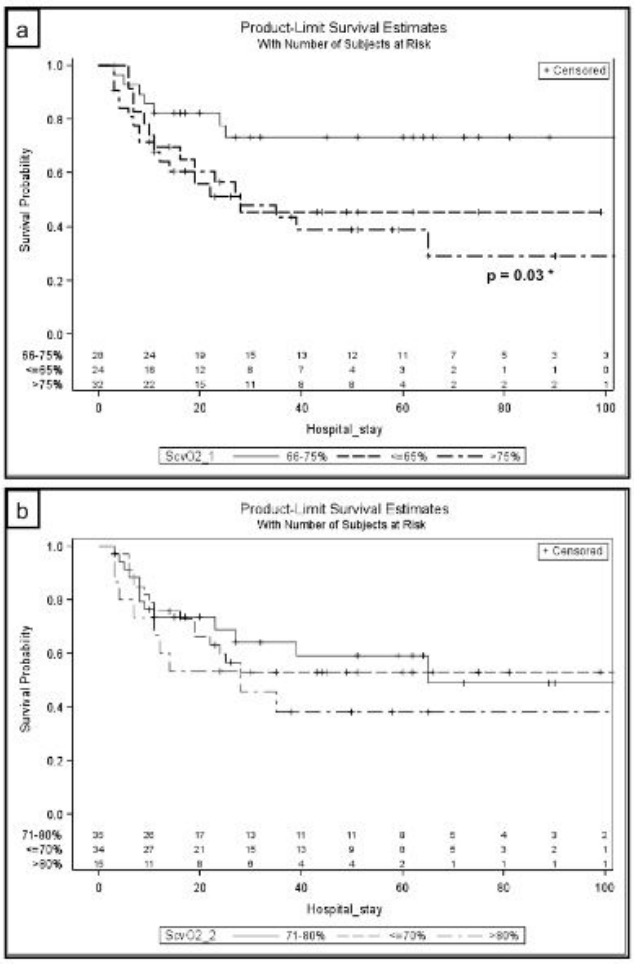

Figure 6: Kaplan Meier curves for septic shock patients stratified by $ScvO_2$ values of third day after ICU admission. (a) Survival curves related to a 66-75% $ScvO_2$ range are in panel and (b) those related to the 71-80% $ScvO_2$ range in panel; $ScvO_2$: Central venous oxygen saturation; *Significant result from adjusted chi-square testing.

On the other hand Park et al. [28] as well as Pope et al. [19] reported significantly elevated in-hospital mortality rates if $ScvO_2$ values and oxygen extraction rates were in the hyperoxic range, i.e., above 89% or lower than 20%, respectively, with the latter most likely indicating $ScvO_2$ values being above 80%. These observations were made within the first hour and after 6 h of ongoing goal directed therapy. The data reported on by Textoris et al. [20] confirmed and extended the period of increased mortality risk in septic patients by investigating maximum $ScvO_2$ values taken during 72 h of treatment, although this group gave no information on the exact time of $ScvO_2$ determination: Using a $ScvO_2$ cut-off value of 80%, a 1.5 fold higher mortality rate for patients with maximum values above 80% was shown compared to those with values below this threshold (48% *vs.* 30%, p<0.05).

Our analysis of mortality rates associated with $ScvO_2$ in the five time intervals using different cut-off values for $ScvO_2$ starting from 65% up to 85% revealed significantly higher mortality rates with $ScvO_2$ values above 75% on the third day. ROC analysis showed an optimal cut-off at 76.0% for third day's $ScvO_2$ (70.4% sensitivity, 60.6%

specificity). Moreover, mortality was significantly higher in patients with $ScvO_2$>75% (n=32) compared to those in the corridor of 66-75% (n=28) on day three with an odds ratio of 3.6 (confidence interval 1.2 to 10.8, p=0.02) (Figure 5). Kaplan-Meier analysis of mentioned $ScvO_2$ corridor on day three confirmed lower survival rates for $ScvO_2$ values below and above the corridor of 66-75%, reaching the level of statistical significance for $ScvO_2$ values above 75% (Figure 6). Thus, patients whose $ScvO_2$ values were in the corridor of 66-75% on third day of septic shock had threefold higher odds of survival compared to those whose $ScvO_2$ was above 75%. This is a drastically lower limit than previously suggested (Pope et al. >90% [19], Textoris et al. >80% [20]) and within the previously recommended range of 70-80% [3,11]. Moreover, these recommendations have been extrapolated to nearly every kind of critical illness, perioperative situations [16,31] and decision-making concerning transfusion [32,33]. According to the present study $ScvO_2$ ranges above 75% have to be considered as potentially deleterious for patients in later stages of septic shock. This is supported by the observation of no single individual, whose $ScvO_2$ was above 85% on the third day of septic shock surviving. Unsurprisingly, specificity of $ScvO_2$ values ≥ 84.0% on day three regarding in-hospital mortality was 100%.

Overall the most important finding was a noticeably increased mortality risk even if $ScvO_2$ values were only slightly elevated (>75%) in later stages of septic shock, which until now have been considered as unsuspicious. They might be used as warning signs as recommended by some authors in the perioperative cardiosurgical setting [24,34].

Limitations

This is a retrospective study. Therefore the observed associations may not be causal and the results have to be confirmed by adequately powered prospective studies. Because the data are from a single center, particularities of local practice may have had an impact on measurement frequency, but also magnitude of $ScvO_2$ values. In addition, $ScvO_2$ measurements were determined for routine care leading to factors of uncertainty such as mix-up of patients and documentation errors. Considering predefined time corridors retrospectively leads to data gaps in some patients because measurements are taken in irregular, clinically necessary and practical intervals. In contrast, for other patients only a fraction of available measurements was used. Incomplete data also result from patients dying during the observation period. Nonetheless we analysed numerous $ScvO_2$ values from septic patients with high mortality risk. In spite of these limitations, we consider it important to disseminate these results because they indicate that potentially harmful $ScvO_2$ levels are apparently very close to formerly recommended treatment goals. In future prospective studies $ScvO_2$ should ideally be measured regularly if not continuously in all patients irrespective of their clinical course. Specifically, in such studies the value of $ScvO_2$ for mortality prediction by U-shaped models should be addressed in a time course dependent fashion.

Conclusion

We strengthened the hypothesis that $ScvO_2$ is of potential value in predicting unfavourable outcome in septic shock. If $ScvO_2$ values of at least 70% have not been achieved within 72 h of therapy, in-hospital mortality significantly increased. On the other hand $ScvO_2$ values above 75% on day three were associated with a threefold mortality rate compared to values in a $ScvO_2$ range of 66-75%. High values in early septic shock seem to be unsuspicious as well as lower ones in later stages. Further investigations have to confirm these findings in before they can be implemented in clinical decision-making.

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Competing Interests

The authors declare that they have no competing interests.

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